

Responses to Major Comments on Technical Support Document

Public Health Goal For Chlorobenzene In Drinking Water

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INTRODUCTION

The following are responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for chlorobenzene as discussed at the PHG workshop held on July 22, 2002, or as revised following the workshop. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from University of California, Riverside

Comment 1: “Given the consistency in the LOAELs for liver responses in the chronic and subchronic studies for different species, a reduction in the subchronic to chronic uncertainty factor or use of a modifying factor might be warranted.”

Response 1: The uncertainty factor used for using a subchronic toxicity study has been reduced from 10 to 3.

Comment 2: “Given the summary data in Table 3, the statement that chlorobenzene has marginal genotoxic potential (page 30) and produces largely negative results in short-term tests (page 24) seem incongruous. I think that it should be emphasized that the positive effects were seen *in vitro* at concentrations at or near the solubility limit of chlorobenzene, and *in vivo* at doses approaching the acute LD₅₀ (1400 mg/kg) in mice. In addition, there appear to be a number of genotoxicity studies which have not been listed. A more extensive listing of genotoxicity studies can be found in the USEPA IRIS document and I would recommend that these be included.”

Response 2: As suggested by the reviewer, several genotoxicity test results described in the U.S. EPA IRIS (2003) were added to the document. In addition, a study reported by Grilli *et al.* (1985) showing that *in vivo* administration of chlorobenzene caused binding of chlorobenzene to DNA and RNA in the liver, kidney, and lung was also included. The discussion of genotoxicity of chlorobenzene and the content of Table 6 were revised.

Comment 3: “A recent metabolism and toxicokinetic study of chlorobenzene in humans has been published [Knecht and Weitowitz (2000) *Int Arch Occup Environ Health* 73:543-54] and the information could be added to page 9 and elsewhere in the text.”

Response 3: The new data have been added to the document.

Comment 4: “The proposed metabolic pathway illustrated in Figure 1 appears to be incorrect based upon the commonly accepted metabolic pathways of other aromatic compounds. The chlorobenzene oxides would be metabolized by epoxide hydrolases to form dihydrodiol metabolites which would then be enzymatically dehydrogenated to form the chlorocatechols. The formation of the chlorocatechols from the chlorophenols as shown would be catalyzed by a second cytochrome P450 catalyzed oxidation.

Response 4: Figure 1 has been revised.

Comments from University of California, Davis (I)

Comment 1: “‘Chronic Toxicity’, it is mentioned that Girard reported one case on human chlorobenzene toxicity. However, the title of the references mentions 7 cases of hematotoxicity due to chlorobenzene derivatives. What were the other 6 cases? Also, what is medullary aplasia?”

Response 1: In the Girard *et al.* paper, only one case was exposed to chlorobenzene. The other 6 cases were exposed to either dichlorobenzene or trichlorobenzene. From the paper (in French), it is not clear what is meant by “d’aplasie médullaire.” The paper was published in May 1969 and the clinical diagnostic terminology used at that time could be different than that of today.

Comment 2: “It could be argued that the NTP study might be the most appropriate one, for several reasons: two species were used and the number of animals per group was considerably higher than in the dog study. The NTP study is comparatively recent, done according to state of the art, thoroughly reviewed and available in the public domain. In both the dog and NTP studies, the NOAEL is about half the LOAEL, the only difference between dogs and rodents being that dogs are apparently more sensitive. The use of a 2 year study would eliminate the inclusion of a uncertainty factor of 10 for short exposure duration. Similarly, the intra-species variability factor - if evidence for this can be found in the NTP study - could probably be reduced to 3.”

Response 2: As shown in Table 6, the subchronic study on dogs reported by Knapp *et al.* (1979) provides the lowest LOAEL of 39 mg/kg-day. This LOAEL is of the same magnitude as the LOAELs (86 mg/kg-day to 103 mg/kg-day) derived from rodent studies, based on liver toxicity through the oral route (Irish, 1963; NTP, 1985, U.S. EPA, 1988a). The difference LOAELs may be attributable to the different study designs or the fact that dogs are more sensitive than rodents to the hepatotoxic effects of chlorobenzene.

The NOAEL value is somewhat dependent on the dose spacing of a study. Although the NOAEL (10.3 mg/kg-day) in a rat study reported by Irish, 1963 is the lowest, the dose spacing of the dog study is closer. As dogs may be more sensitive than rodents to chlorobenzene exposure, the NOAEL (19 mg/kg-day) derived from the dog study was selected as the basis for quantitative risk assessment.

Given the apparent similarity in the LOAELs for liver toxicity observed in the subchronic and chronic rat studies reported (NTP, 1985; Irish, 1963; U.S. EPA, 1988a), the uncertainty factor for short-term exposure has been reduced from 10 to 3.

Comments from University of California, Davis (II)

Comment 1: “I found the document to be incomplete in its reporting of the process used to generate the parameter estimates used in the calculation of the PHG.”

Response 1: The estimates of an adult body weight of 70 kg and a relative source contribution of 0.2 used in the risk assessment are defaults recommended by U.S. EPA

and OEHHA risk assessment guidelines, as discussed in more detail in EPA (2002) and OEHHA (2000). The daily water consumption rate was assumed to be 4 Lq/day instead of the default of 2 Lq/day because multi-route combined exposure estimates for volatile halogenated solvents typically yield values of this magnitude. This estimate combines exposures derived from all household uses of the contaminated water (e.g., cooking, showering, and bathing), by the oral, dermal, and inhalation exposure routes. Although the rationale for these and other parameters could be, and in some PHG documents have been, explained more thoroughly, it is probably more useful to go to the general risk assessment literature for good discussions of these common or default assumptions.

Comment 2: “Despite the use of uncertainty factors in the analysis, there is essentially no discussion of the uncertainties involved in the analysis used to establish the PHG. It should be noted that describing the uncertainty factors used in the calculations is not equivalent to a discussion of the uncertainties involved in the setting of the PHG. The relationship between the use of the uncertainty factors and parameter uncertainty is important but is only a small portion of a discussion of the uncertainty in the analysis.”

Response 2: OEHHA acknowledges that the discussion of parameter uncertainty is minimal, and agrees with the reviewer’s comment. We have not discussed, for example, uncertainty about the shape of a dose-response curve for the critical effects in the dog study used for estimating the health-protective level. We have also not addressed relative uncertainty in determining whether chlorobenzene might cause cancer in humans, considering its similarity to well-known human carcinogens such as benzene. However, we think that the level of discussion about uncertainty in this risk assessment is appropriate for this particular evaluation and its intended usage. A quantitative uncertainty analysis including detailed discussion of scenario and model uncertainty in addition to parameter uncertainty is generally not performed for PHG evaluations.

REFERENCES

OEHHA (2002). Technical Support Document for Exposure Assessment and Stochastic Analysis. Air Toxics Hot Spots Program Risk Assessment Guidelines, Part IV. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland and Sacramento, CA.

U.S. EPA (2002). A Review of the Reference Dose and Reference Concentration Processes. External Review Draft. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. EPA/630/P-02/002A.